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Aerobic oxidation of β-isophorone by tetraphenylporphyrin catalysts in pyridine solution

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ABSTRACT

A kinetic study was conducted using five metallo-tetraphenylporphyrins (MTPPs) as catalysts for the aerobic oxidation reaction of β-isophorone (β-IP) to ketoisophorone (KIP). The oxidation reaction catalyzed by MTPPs (M = Cr, Mn, Fe, Co and Cu) was observed over a seven hour period under a range of experimental conditions. Changes in the specificity of conversion of reactant to the product, KIP, and the main side-product, α-isophorone (α-IP), were observed at temperatures ranging from 60 °C to 75 °C, in solvents with varying compositions of pyridine and β-IP, with different MTPP catalysts, oxygen gas flow rates, and solution agitation frequencies. Control experiments show that MTPP catalysts modestly increase the rate of KIP formation, but significantly improve specificity through the apparent suppression of α-IP formation. Analysis revealed that MnTPP (CH_3COO^-) produced the highest product specificity ratio [KIP]/[α-IP]. Given that all of the metals were in the 3+ oxidation state in this study and there was no observed binding by O_2 to any of the MTPP catalysts, the catalytic mechanism is suggested to involve the binding of β-IP to the MTPP metal center. Binding of β-IP is most favorable when pyridine is the trans ligand, but β-IP is also observed to weakly bind when trans to acetate in the MnTPP adduct. This conclusion is supported by electronic absorption spectroscopy, resonance Raman spectroscopy and density functional theory (DFT) calculations. The role played by the catalyst appears to be the activation of hydrogen abstraction following the substrate's ligation to the metal, rather than the more traditional role of MTPPs as O_2 activation catalysts by ligation of diatomic O_2. β-IP oxidation is an example of a case where the catalyst appears to have a more important role for improving the specificity of the reaction (through decreasing side-product formation) rather than increasing the rate of product formation.

1. Introduction

Recently, the push for more environmentally friendly or "green" chemistry has prompted exploration of oxidation by diatomic O_2 in air [1–4]. Diatomic O_2 is attractive because of its abundance and availability, but the limitation of the partial pressure of O_2 in air requires greater emphasis on studying the catalytic mechanism in order to optimize the process. First row transition metal catalysts – such as Co, Mn, Cr, Cu, Fe, and V – have been extensively researched in the bonding and activation of oxygen for oxidation reactions, but systematic comparisons of their reactivity are still needed in order to understand the factors that optimize reaction rates [5]. Cu and Fe dominate biological oxygen chemistry and catalysis, with both being desirable from an environmental point of view as well. Clearly, many of the first tow transition elements are also abundant and environmentally compatible, which further motivates systematic study of their catalytic mechanisms.

Ketoisophorone (KIP, 3,3,5-trimethyl-cyclohex-2-ene-1,4-dione) is an important chemical intermediate used for a variety of important reactions, including vitamin E [1] and carotenoid [2] synthesis. The common precursor for KIP is isophorone, which is found in both the conjugated α (α-IP, 3,3,5-trimethyl-cyclohex-2-enone)

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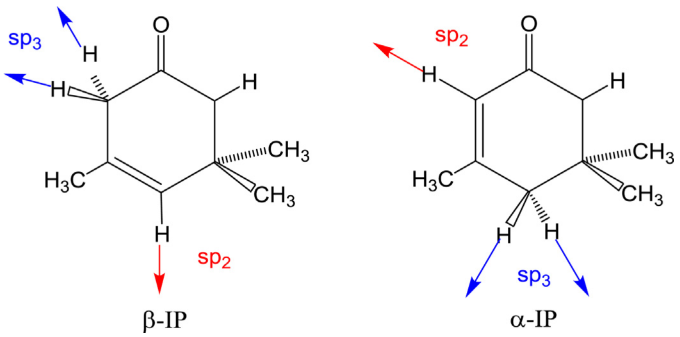

Fig. 1. Structures of β-IP and α-IP showing the hybridization of the carbon atoms from which hydrogen abstraction occurs. The sp$_3$ sites were considered to be energetically equivalent although they may not be sterically equivalent under reaction conditions.

and the unconjugated β (β-IP, 3,3,5-trimethyl-cyclohex-3-enone) forms. Although, α-IP is a more readily available compound, the unconjugated isomer, β-IP is thermodynamically higher in energy and thus is more readily oxidized. Computational analysis [6] reveals significantly lower C—H bond dissociation energies for β-IP, especially at the sp^3 position of β-IP shown in Fig. 1. The radical intermediate of β-IP in this position is also stabilized by π-conjugation [5,6]. Since β-IP can be produced by high temperature distillation of the equilibrium mixture of α-IP and β-IP, it is readily available as a starting material. The major obstacle to the use of β-IP from a practical point of view is the spontaneous conversion of β-IP into the thermodynamically more stable α-IP, which is a side reaction that competes with KIP formation. The role of any catalyst for this oxidation reaction is to accelerate the formation of KIP and, perhaps more importantly, to enhance the selectivity of the reaction by increasing the ratio of [KIP]/[α-IP] in the resulting product mixture.

The oxidation of β-IP to KIP is known using various transition metal (Mn, Co, Cu) catalysts based on the ligands bis-salicylaldehyde ethylenediimine (salen) [1,4] and (bis-salicylaldehyde (sal) [5]. The rate equation for β-IP → KIP oxidation was determined to be $\text{rate} = k[\text{Cat}][\beta\text{-IP}][O_2]^{1/2}$ for these systems, where Cat is the catalyst [7]. The overall reaction order according to this analysis is 2.5 over the temperature range from 10 to 27 °C [1]. In the present study, we have focused on the role of the metal using MTPP catalysts with kinetic assays, spectroscopic studies and DFT calculations. Although β-IP is the more common starting material, several attempts have been made to synthesize KIP directly from α-IP using catalytic radical reactions that do not involve metals [8–11]. Despite some promising results, KIP formation directly from α-IP is slow under all conditions reported thus far. Comparative experimental data between similar α-IP and β-IP radical oxidation reactions show that β-IP oxidation is significantly more efficient than α-IP oxidation, with higher yields and product specificity [6,8]. Catalysis using metal(salen) complexes show similar benefits for using β-IP over α-IP [12]. However, some exceptions are known. For example, it has been reported that Ru(IV) tetraphenylporphyrin (TPP) efficiently catalyzes α-IP oxidation, forming 99% KIP after 8 h [13]. At the present time the significant thermodynamic advantages of β-IP results in it being the only useful starting material for large-scale syntheses of KIP. Therefore, β-IP is still the main focus of mechanistic studies of KIP synthesis, with studies that utilize α-IP remaining relatively rare [8–10].

While elevated temperatures (>110 °C) [12] and strong oxidants (such as *tert*-butyl hydroperoxide) have been used for β-IP oxidation [6,12], there has also been some progress towards the inexpensive syntheses of KIP in air using more moderate temperatures [8,9]. The majority of research on β-IP oxidation is focused on catalysis by transition metal compounds in the absence of initiator [5,7,12,14]. Thus, either O_2 itself or an activated form of O_2 that is bound to the catalyst must abstract a hydrogen atom to serve as the initiator for a radical mechanism. Metal tetraphenylporphyrins (MTPPs) and similar macrocyclic compounds are well known for their oxygen activation properties [14,15], but O_2 can form a complex with the MTPP catalysts only if the metal is in a reduced (M^{2+}) state. For this reason, recent oxidation studies of related substrates catalyzed by Mn porphyrins have used H_2O_2, HOCl or iodosylbenzene as the oxidant [16–18]. Both experimental and computational data from the present study suggest that this reduction is not favorable for either α-IP or β-IP and therefore an alternative mechanism must be operative, which we propose involves ligation by the substrate to the metal of MTPP. There are other reactions by MTPPs, which produce intermediates with reactivity towards C—H bonds, such as a halogenation reaction catalyzed MnTPPCl [19].

One attractive feature of the porphyrin scaffold is the ability to compare different metal ions in order to gain insight into the catalytic mechanism. Moreover, MTPPs have produced some of the most promising results under conditions of ambient temperature using the O_2 in air as the oxidant. In particular, MnTPP [20] and Cu-DSALA [21] have been demonstrated to produce excellent yields of 93% and 95%, respectively. However, despite the widespread use of MTPP and related compounds for the oxidation of either isomer of isophorone there remains a paucity of kinetic analyses or this class of catalytic reactions [5].

The proposed mechanism for the oxidation of β-IP with a MTPP catalyst in air (Fig. 2) can follow two possible pathways involving radical intermediates. The role of the catalyst is slightly different in both mechanisms, as is the requirement for an external base. However, both involve isomerization of the radical once formed and addition of diatomic O_2 to a radical in order to form a deoxygenated intermediate. We call these two possible mechanisms the enolate-electron transfer and hydrogen abstraction mechanisms, as indicated in Fig. 2.

The hydrogen abstraction mechanism (Fig. 2—right) involves immediate formation of a β-IP radical through elimination of the α-hydrogen. In the absence of a catalyst, there is a significant yield of this product, suggesting that O_2 itself can act as the oxidant for this transformation. However, in the uncatalyzed reaction isomerization to form α-IP competes with the formation of the oxidation product resulting in poor overall yields of KIP. In this work we find that one role of the MTPP catalysts is to modestly increase the rate of KIP formation. However, we find a significant decrease in the yield of α-IP in all cases versus the uncatalyzed reaction. The free radical IP formed by H-abstraction in the α position (see Fig. 2) has a resonance structure in the γ position. Addition of O_2 at the γ position is on the pathway to form KIP, but addition of H directly forms α-IP. In the enolate electron transfer pathway, the α-hydrogen atom is abstracted by base (shown in Fig. 2 as pyridine) to yield the enolate. If the energetics are favorable, the radical can be formed by electron transfer from the enolate to the MTPP catalyst.

Solvents have also played a significant role in the catalyzed isophorone reaction. While there is general agreement that aprotic solvents are beneficial for the rate [4,5,6,21], pyridine has been shown to be the optimum solvent for the reaction [4,21] despite the fact that it is known to reduce selectivity for KIP formation in other reactions [5,21]. Unfortunately, a role for solvent has not been explained in previous studies. One important consequence of the oxidation of β-IP (or α-IP) with O_2 is the generation of stoichiometric H_2O, which results in a change in solvent polarity during the course of the reaction. This significant change in solvation and acid-base chemistry should be considered in the explanation of the observed kinetic profile. Our goal in this study